

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :
Valerie AUTIER et al. : Group Art Unit.: 1614
Serial No.: 10/541,377 : Examiner: HUGHES, Alicia R.
Filed: July 6, 2005 :
Title: KYNURENINE 3-HYDROXYLASE INHIBITORS FOR THE TREATMENT OF
DIABETES

APPEAL BRIEF

Mail Stop: AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed on September 29, 2008, please consider the following.

The Appeal Brief fee of \$ 540.00 is filed/paid herewith.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

(i) REAL PARTY IN INTEREST

The real party in interest is Merck Patent Gesellschaft.

(ii) RELATED APPEALS AND INTERFERENCES

There are no known related appeals or interferences.

(iii) STATUS OF CLAIMS

Claims 16, 27-28 and 30-46 are pending in the present application.

Claims 1-15, 17-26 and 29 were cancelled.

No claims were withdrawn from consideration.

No claims were allowed.

Claims 16, 27-28 and 30-46 were rejected.

Claims 16, 27-28, 30-39 and 44-46 are on appeal.

(iv) STATUS OF AMENDMENTS

Amendments were filed after the final rejection on August 20, 2008 and on August 21, 2008.

The Advisory Action dated October 24, 2008, provides reasons only for the non-entry of the amendments filed on August 21, 2008, with which reasons applicants respectfully disagree.

Apparently however, none of the above amendments were entered since said Advisory Action cites claims 16, 27-28 and 30-46 as pending in the present application, while the amendments filed on August 20, 2008 attempted to cancel claims 40-43.

No comments were provided why the amendments filed on August 20, 2008, attempting to cancel claims 40-43 (which recited prodrugs), attempting to delete prodrugs from claim 34, and correcting dependencies of dependent method claims to be dependent from the independent method claim 16 instead of the independent product claims 34, were not entered. Applicants are in the position that the amendments filed on August 20, 2008, would have only simplified the appeal.

Nevertheless, without prejudice or disclaimer, to keep the appeal process simple and directed to the rejection of concern, applicants do not appeal the rejections based on

“prodrugs” and under section 112, second paragraph, for lack of antecedent basis for the dependent method claims which incorrectly depended from the independent product claims.

Instead, applicants will have these amendments entered after the appeal process has concluded.

(v) SUMMARY OF CLAIMED SUBJECT MATTER

Appellants’ invention recited in independent claim 16 is directed to method for treating diabetes or a complication thereof by the administration of one of several specific compounds recited in said claim. See specification page 1, lines 5-8, page 3, line 22 to page 5, line 16, page 27, line 25 to page 30, line 2, and pages 39-42 and 44-45.

Appellants’ invention recited in independent claim 34 is directed to specific compounds. See page 27, line 25 to page 30, line 2, and pages 39-42 and 44-45.

(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The ground for rejection is the rejection under 35 U.S.C. § 103, i.e., whether claims 16, 27-28, 30-39 and 44-46 are obvious over US 6,323,240 in view of US 6,572,542.

(vii) ARGUMENT

The claims of the present application recite specific 2-... **thio**-...-oxobutanoic group containing compounds. That is, an S group is attached in position 2 of the claimed compounds with further groups attached to said S group. See, e.g., the compounds depicted by structure in the specification on pages 39-42 and 44-45. Neither reference teaches or suggests any compound with a thiol group, and definitely not any of the specific compounds recited in the claims.

US '240 in its broadest disclosure recites thiol as one of the many options for any of R₁ through R₄. See column 2, lines 40-50 and line 61-64. However, not a single compound with a thiol group is taught in the disclosure of the reference. Moreover, not a single thiol group even apart from an overall structure is identified in US '240. Merely, a broad recitation of "thiol" is made in the disclosure of US '240.

Although not necessary to define the meaning of "thiol" as such definition is not in dispute and is well known to be a group represented by the formula RSH, where R can be another radical without limitations, applicants point out that previously provided to the Examiner were dictionary definitions of this term in arguments as follows:

The definition of thiol is "a sulfur-containing organic compound having the general formula RSH, where R is another element or radical ... Also called mercaptan." (Emphasis added.) See The American Heritage® Science Dictionary, Copyright © 2002 by Houghton Mifflin Company, Published by Houghton Mifflin Company. Mercaptan is defined as a "sulfur-containing organic compound with the general formula RSH where R is any radical, especially ethyl mercaptan, C₂H₅SH. Also called thiol." (Emphasis added.) See The American Heritage® Dictionary of the English Language, Fourth Edition, Copyright © 2006 by Houghton Mifflin

See Reply filed on August 20, 2008.

Thus, one of ordinary skill in the art would understand the disclosure of US '240 when reciting "thiol" as reciting a group RSH with any R group attached to the S group, and no contrary allegations are made on the record.

However, a broad recitation of "any" group in a given position is not adequate to render obvious the specific compounds of the present claims. For example, in claim 16, the first named compound has a benzyl group attached to the S group, the second named compound has a methylphenyl group attached to the S group, etc. No such groups are described in US '240 with any specificity. One of ordinary skill in the art would thus not have found a reason to select, e.g., benzyl or methylphenyl, etc., groups attached to the S group.

In sum, the prior art general formula at issue here generically encompasses an extremely large number of individual compounds, especially so in view of any group being possible as the R group in a thiol group, in case a thiol group would have been selected from the generic disclosure for position 2, for which selection there is also no reason provided in US '240.

In a situation like this, the non-obviousness of the claimed compounds is controlled by long standing strong Federal Circuit precedent. Exemplary such Federal Circuit cases include *In re Jones*, 958 F.2d 347, 21 U.S.P.Q. 2d 1941 (Fed. Cir. 1992) and *In re Baird*, 16 F.2d 380, 29 U.S.P.Q. 2d 1550 (Fed. Cir. 1994).

In both *Jones* and *Baird*, the general disclosures of the references encompassed a very large number of individual compounds.

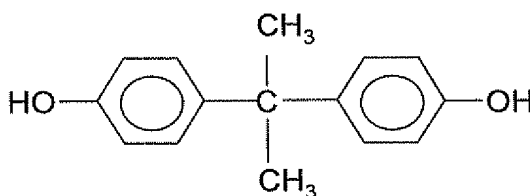
In *Jones* the Federal Circuit held that:

We decline to extract from *Merck* the rule that the Solicitor appears to suggest – that regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it. ... In contrast, though Richter discloses the potentially infinite genus of “substituted ammonium salts” of dicamba, and lists several such salts, the salt claimed here is not specifically disclosed. Nor, as we have explained above, is the claimed salt sufficiently similar in structure to those specifically disclosed in Richter as to render it *prima facie* obvious. (21 U.S.P.Q. 2d at 1943)

While the claimed compounds may fall within the scope of US ‘240, there is no reason for one of ordinary skill in the art to select any of them from among the very large number of compounds generically encompassed. There is no specific disclosure in US ‘240 which would lead one of ordinary skill in the art to prepare any of the claimed compounds; for example, nothing provides a reason to a skilled worker to make a compound, e.g., with a benzylthio group, or a methylphenylthio group, ..., naphthylthio group, etc. Without any reason provided for the preparation of such compounds, there cannot be a *prima facie* case of obviousness in view of *Jones* and many other decisions on this issue.

The lack of obviousness in the present case is even stronger than in, e.g., *Baird*.

Baird’s claimed compounds had the following structure:



wherein each of the two OH-groups was esterified with one of three dicarboxylic acids (succinic (4 carbon atoms), glutaric (5 carbon atoms) or adipic (6 carbon atoms).) The reference had a very broad general formula encompassing, in very general terms, compounds possessing both components of Baird's claims, i.e., the above-pictured central diphenyl moiety (bisphenol A) and the terminal dicarboxylic acid esterifying groups. However, the general formula also disclosed the possibility of highly varied substitution on each of the phenyl rings, the possibility that the central three carbon atom propyl moiety to which each phenyl group is joined in the bisphenol A structure pictured above could instead also be a very wide variety of groups such as other alkylene groups, alkylidene groups or cycloalkylidene groups. Instead of the hydroxy groups at the terminal positions of bisphenol A, the phenyl rings in the reference could also be any of a large variety of possibilities, where between the O atom and the H atom of hydroxyl, there could be present (RO)_x groups which were the same or different. The reference also specifically named, among twenty typical dicarboxylic acids for esterification, the three recited in Baird's claim.

The Court in *Baird* relied on the *Jones* holding quoted above, to quickly dismiss the Patent and Trademark Office's contention that the generally encompassing formula alone was sufficient to render Baird's claimed species obvious. The Court concluded that given (a) the vast number of diphenols encompassed by the reference's general disclosure, and (b) that the mentioned diphenols more specifically disclosed by the reference as typical, preferred or optimum were different from *Baird's* bisphenol A structure, the reference did not suggest the selection of bisphenol A.

Here, not even a specific disclosure as in *Baird* is present. All the compounds identified in US '240 are compounds which do not contain a thiol group in any position.

More recent Federal Circuit decisions post dating *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385 (2007) specifically discuss the requirements of

establishing obviousness, especially in the chemical arts, and further confirm that there cannot be obviousness in the present case. See, e.g., the decisions of the Federal Circuit in *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007), and *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd. et al.*, 87 USPQ2d 1452 (Fed. Cir. 2008).

One of the issues in *Takeda* was whether picking a specific compound as a starting point (lead compound) from the prior art disclosing it and several others is obvious without a reason leading to its choice. The Federal Circuit's answer was no.

The prior art reference in *Takeda* taught the exact same use for the compounds as claimed in the later application (antidiabetic treatment), taught 34 compounds specifically from a broad generically disclosed formula, including the specific compound of interest in the later application, the prosecution history of the prior art reference supplied test data for nine specific compounds, including the specific compound of interest, the compound of interest was specifically claimed in one of the patents in the prior art patent family, i.e., a claim specifically was directed to the compound of interest alone (see claim 4 of US 4,444,779), and the prosecution history thereof included a statement to the effect that the claimed compounds became important, especially the compound of interest.

A separate prior art document tested 101 various prior art compounds, including the compound of interest, and indicated some side effects associated with the compound of interest.

The lower court held, which holding was upheld by the Federal Circuit, that the selection of the compound of interest as a lead compound was not obvious in view of the prior art. The lower court held that any "suggestion to select" the compound of interest was negated by the separate prior art document testing various prior art compounds. (Emphasis added.) The Federal Circuit rejected arguments relying on *KSR* that "the claimed compounds would have been obvious because the prior art compound fell within 'the objective reach of

the claims.’”

Thus, it is clear that the law requires “suggestion to select” the compounds of interest from the prior art, and it is not adequate that a compound merely fall within the objective reach of a claim.

The Federal Circuit in *Eisai* characterized the holding of *Takeda* by stating that “obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e., a lead compound) in a particular way to achieve the claimed compound.” Emphasis added.

The court went on to summarize the state of the law of obviousness, especially as it pertains to chemical arts, as follows:

First, KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might **identify a problem and pursue potential solutions**. Second, KSR presupposes that the record up to the time of invention would **give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound.** See Takeda, 492, F.3d at 1357 (“Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.”). Third, the Supreme Court’s analysis in KSR presumes that the record before the time of invention would **supply some reasons for narrowing the prior art universe to a “finite number of identified, predictable solutions,”** 127 S. Ct. at 1742. In Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that

this “easily traversed, small and finite number of alternatives . . . might support an inference of obviousness.”

To the extent an art is unpredictable, as the chemical arts often are, KSR’s focus on these “identified, predictable solutions” may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.

(Emphasis added.)

The compound of the claims in *Eisai*, i.e., Lansoprazole, was in an art where the core of the compound was known and described in a class of compounds by a reference, i.e., Brändström. Rabeprazole, a specific prior art compound, had the same core and substituents thereon with the exception of an $\text{OCH}_2\text{CH}_2\text{CH}_2\text{OCH}_3$ group in the 4-position, where the claimed Lansoprazole has an OCH_2CF_3 group. Omeprazole, another compound sharing the same core has an OCH_3 group in the 4-position. The Federal Circuit even taking the evidence most favorable to the movant on Summary Judgment challenging the validity of the patent did not find obviousness. There was evidence in the record that the fluorinated substituent on the lead, i.e., Lansoprazole, which was selected as the allegedly obvious lead by the movant, provided a special path to achieving lipophilicity. Without discernible reason on the record why one of ordinary skill in the art would have modified this group, which was known to provide lipophilicity, the Federal Circuit held that there was no obviousness.

In the present case besides the broad recitation of “thiol” as possible substituent for any of R_1 to R_4 , nothing therein even remotely teaches or suggests any of the compounds of the present claim. Thus, the rejection has not complied with the necessity of identifying some reason that would have led a chemist to modify a known compound from the prior art in a particular manner to establish the prima facie obviousness of the presently claimed new compounds. Moreover, the rejection does not supply any reason for narrowing the prior art universe (which includes all thiol groups with any R group in the RSH moiety) to a “finite

number of identified, predictable solutions.” As such, there cannot be obviousness over the disclosure of US ‘240.

Moreover, in US ‘240 alkylthio is also an option for R₁ through R₄, and a specific compound with either R₁ or R₃ being thiomethyl is prepared (see column 5, line 47). However, alkylthio groups are irrelevant to rendering any thiol group obvious. Such a compound explicitly teaches away from a compound where the S group is attached directly at the 2 position of the compound as in said compound the alkyl group is attached to the 2 position.

US ‘542 does not overcome the deficiencies of US ‘240 as it provides nothing regarding the claimed compounds or possible modifications thereto. Moreover, no such allegations are made.

Reversal of the rejection is respectfully and courteously requested.

Respectfully submitted,

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(viii) CLAIMS APPENDIX

16. A method for treating diabetes or a complication thereof comprising administering to a patient in need thereof an effective amount of one of the following compounds

- 2-benzylthio-4-phenyl-4-oxobutanoic acid;
- 2-(4'-methylphenylthio)-4-phenyl-4-oxobutanoic acid;
- 2-(4'-chlorophenylthio)-4-phenyl-4-oxobutanoic acid;
- 2-(4'-fluorophenylthio)-4-phenyl-4-oxobutanoic acid;
- 2-(4'-methoxyphenylthio)-4-phenyl-4-oxobutanoic acid;
- 2-phenylthio-4-phenyl-4-oxobutanoic acid;
- 2-carboxymethylthio-4-phenyl-4-oxobutanoic acid;
- 2-cyclohexylthio-4-phenyl-4-oxobutanoic acid;
- 2-(2'-naphthylthio)-4-phenyl-4-oxobutanoic acid;
- ethyl 2-phenylthio-4-phenyl-4-oxobutanoate;
- ethyl 2-(4'-fluorophenylthio)-4-phenyl-4-oxobutanoate;
- ethyl 2-(4'-chlorophenylthio)-4-phenyl-4-oxobutanoate;
- ethyl 2-(4'-methylphenylthio)-4-phenyl-4-oxobutanoate;
- ethyl 2-(4'-methoxyphenylthio)-4-phenyl-4-oxobutanoate;
- ethyl 2-(2'-naphthylthio)-4-phenyl-4-oxobutanoate;
- ethyl 2-cyclohexylthio-4-phenyl-4-oxobutanoate;
- ethyl 2-benzylthio-4-phenyl-4-oxobutanoate;
- 2-phenylthio-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-(4'-fluorophenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-(4'-chlorophenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-(4'-methylphenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-(4'-methoxyphenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-(2'-naphthylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-cyclohexylthio-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-benzylthio-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-phenylthio-4-(4'-chlorophenyl)-4-oxobutanoic acid;
- 2-(4'-fluorophenylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid;

- 2-(4'-methylphenylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid;
 - 2-(4'-methoxyphenylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid; or
 - 2-(2'-naphthylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid;
- or a geometrical or optical isomer thereof,
 or a tautomeric form thereof;
 or a solvate or hydrate thereof,
 or a salt thereof with a pharmaceutically acceptable acid or base.

27. A method according to Claim 16, wherein the risk of hypoglycaemia is reduced.

28. A method according to Claim 16, wherein non-insulin-dependent diabetes or a complication thereof is treated.

30. A method according to claim 16, wherein the compound administered is capable of the inhibition of kynurenine 3-hydroxylase.

31. A method according to claim 16, wherein the compound administered is capable of the inhibition of kynurenine 3-hydroxylase in an *in vitro* test.

32. A method according to claim 16, wherein diabetes is treated.

33. A method according to claim 16, wherein a complication of diabetes is treated.

34. A compound, which is

- 2-benzylthio-4-phenyl-4-oxobutanoic acid;
- 2-(4'-methylphenylthio)-4-phenyl-4-oxobutanoic acid;
- 2-(4'-chlorophenylthio)-4-phenyl-4-oxobutanoic acid;
- 2-(4'-fluorophenylthio)-4-phenyl-4-oxobutanoic acid;
- 2-(4'-methoxyphenylthio)-4-phenyl-4-oxobutanoic acid;
- 2-phenylthio-4-phenyl-4-oxobutanoic acid;
- 2-carboxymethylthio-4-phenyl-4-oxobutanoic acid;

- 2-cyclohexylthio-4-phenyl-4-oxobutanoic acid;
- 2-(2'-naphthylthio)-4-phenyl-4-oxobutanoic acid;
- ethyl 2-phenylthio-4-phenyl-4-oxobutanoate;
- ethyl 2-(4'-fluorophenylthio)-4-phenyl-4-oxobutanoate;
- ethyl 2-(4'-chlorophenylthio)-4-phenyl-4-oxobutanoate;
- ethyl 2-(4'-methylphenylthio)-4-phenyl-4-oxobutanoate;
- ethyl 2-(4'-methoxyphenylthio)-4-phenyl-4-oxobutanoate;
- ethyl 2-(2'-naphthylthio)-4-phenyl-4-oxobutanoate;
- ethyl 2-cyclohexylthio-4-phenyl-4-oxobutanoate;
- ethyl 2-benzylthio-4-phenyl-4-oxobutanoate;
- 2-phenylthio-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-(4'-fluorophenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-(4'-chlorophenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-(4'-methylphenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-(4'-methoxyphenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-(2'-naphthylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-cyclohexylthio-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-benzylthio-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-phenylthio-4-(4'-chlorophenyl)-4-oxobutanoic acid;
- 2-(4'-fluorophenylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid;
- 2-(4'-methylphenylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid;
- 2-(4'-methoxyphenylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid; or
- 2-(2'-naphthylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid;

or a geometrical or optical isomer thereof,

or a tautomeric form thereof;

or a solvate or hydrate thereof,

or a salt thereof with a pharmaceutically acceptable acid or base,

or a pharmaceutically acceptable prodrug thereof.

35. A method according to claim 16, comprising administering to a patient in need thereof an effective amount of one of the following compounds

- 2-benzylthio-4-phenyl-4-oxobutanoic acid;

- 2-(4'-methylphenylthio)-4-phenyl-4-oxobutanoic acid;
 - 2-(4'-chlorophenylthio)-4-phenyl-4-oxobutanoic acid;
 - 2-(4'-fluorophenylthio)-4-phenyl-4-oxobutanoic acid;
 - 2-(4'-methoxyphenylthio)-4-phenyl-4-oxobutanoic acid;
 - 2-phenylthio-4-phenyl-4-oxobutanoic acid;
 - 2-carboxymethylthio-4-phenyl-4-oxobutanoic acid;
 - 2-cyclohexylthio-4-phenyl-4-oxobutanoic acid;
 - 2-(2'-naphthylthio)-4-phenyl-4-oxobutanoic acid;
 - ethyl 2-phenylthio-4-phenyl-4-oxobutanoate;
 - ethyl 2-(4'-fluorophenylthio)-4-phenyl-4-oxobutanoate;
 - ethyl 2-(4'-chlorophenylthio)-4-phenyl-4-oxobutanoate;
 - ethyl 2-(4'-methylphenylthio)-4-phenyl-4-oxobutanoate;
 - ethyl 2-(4'-methoxyphenylthio)-4-phenyl-4-oxobutanoate;
 - ethyl 2-(2'-naphthylthio)-4-phenyl-4-oxobutanoate;
 - ethyl 2-cyclohexylthio-4-phenyl-4-oxobutanoate;
 - ethyl 2-benzylthio-4-phenyl-4-oxobutanoate;
 - 2-phenylthio-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
 - 2-(4'-fluorophenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
 - 2-(4'-chlorophenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
 - 2-(4'-methylphenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
 - 2-(4'-methoxyphenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
 - 2-(2'-naphthylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
 - 2-cyclohexylthio-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
 - 2-benzylthio-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
 - 2-phenylthio-4-(4'-chlorophenyl)-4-oxobutanoic acid;
 - 2-(4'-fluorophenylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid;
 - 2-(4'-methylphenylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid;
 - 2-(4'-methoxyphenylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid; or
 - 2-(2'-naphthylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid;
- or a salt thereof with a pharmaceutically acceptable acid or base.

36. A method according to claim 34, wherein the risk of hypoglycaemia is

reduced.

37. A method according to claim 34, wherein non-insulin-dependent diabetes or a complication thereof is treated.

38. A method according to claim 34, wherein diabetes is treated.

39. A method according to claim 34, wherein a complication of diabetes is treated.

44. A method according to claim 34, comprising administering to a patient in need thereof an effective amount of one of the following compounds

- 2-benzylthio-4-phenyl-4-oxobutanoic acid;
- 2-(4'-methylphenylthio)-4-phenyl-4-oxobutanoic acid;
- 2-(4'-chlorophenylthio)-4-phenyl-4-oxobutanoic acid;
- 2-(4'-fluorophenylthio)-4-phenyl-4-oxobutanoic acid;
- 2-(4'-methoxyphenylthio)-4-phenyl-4-oxobutanoic acid;
- 2-phenylthio-4-phenyl-4-oxobutanoic acid;
- 2-(2'-naphthylthio)-4-phenyl-4-oxobutanoic acid;
- ethyl 2-phenylthio-4-phenyl-4-oxobutanoate;
- ethyl 2-(4'-fluorophenylthio)-4-phenyl-4-oxobutanoate;
- ethyl 2-(4'-chlorophenylthio)-4-phenyl-4-oxobutanoate;
- ethyl 2-(4'-methylphenylthio)-4-phenyl-4-oxobutanoate;
- ethyl 2-(4'-methoxyphenylthio)-4-phenyl-4-oxobutanoate;
- ethyl 2-(2'-naphthylthio)-4-phenyl-4-oxobutanoate;
- ethyl 2-benzylthio-4-phenyl-4-oxobutanoate;
- 2-phenylthio-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-(4'-fluorophenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-(4'-chlorophenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-(4'-methylphenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-(4'-methoxyphenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-(2'-naphthylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- 2-benzylthio-4-(4'-methoxyphenyl)-4-oxobutanoic acid;

- 2-phenylthio-4-(4'-chlorophenyl)-4-oxobutanoic acid;
 - 2-(4'-fluorophenylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid;
 - 2-(4'-methylphenylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid;
 - 2-(4'-methoxyphenylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid; or
 - 2-(2'-naphthylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid;
- or a salt thereof with a pharmaceutically acceptable acid or base.

45. A method according to claim 34, comprising administering to a patient in need thereof an effective amount of one of the following compounds

- 2-carboxymethylthio-4-phenyl-4-oxobutanoic acid;
- or a salt thereof with a pharmaceutically acceptable acid or base.

46. A method according to claim 34, comprising administering to a patient in need thereof an effective amount of one of the following compounds

- 2-cyclohexylthio-4-phenyl-4-oxobutanoic acid;
 - ethyl 2-cyclohexylthio-4-phenyl-4-oxobutanoate; or
 - 2-cyclohexylthio-4-(4'-methoxyphenyl)-4-oxobutanoic acid;
- or a salt thereof with a pharmaceutically acceptable acid or base.

(ix) EVIDENCE APPENDIX

None

(x) RELATED PROCEEDINGS APPENDIX

None